P.G. Sem II CC7 Unit-3 submit. 3.5

Free Fatty Acid Synthesis & Importance (Part-I)

Fatty Acids are synthesized when total energy intake, in the form of Carbohydrate, Proteins and Lipids as food constituents, is higher than the total energy utilized from enzymatic oxidation of these components. Synthesis of fatty acids occurs in Liver, mammary glands of lactating mothers and also, in adipose tissue and kidneys. Oxidation of fatty acids generate acetyl CoA; Conversely, acetyl CoA is utilized in fatty acid synthesis, but the two processes are not in toto reversal of each other. They differ from each other in many aspects, such as nature of enzymes and coenzymes, their intracellular locations and nature of intermediary metabolites.

Fatty acids are synthesized in cytosol from acetyl CoA produced from different pathways such as β-oxidation of fatty acids in mitochondria, oxidative decarboxylation of pyruvate in mitochondria and degradation of amino acids in cytosol.

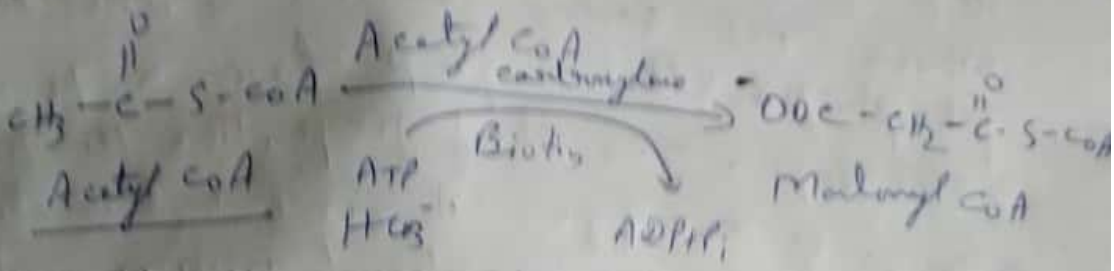
Step 1: Transport of Acetyl CoA from mitochondria to Cytosol — Although fatty acid synthesis occurs in cytosol most of acetyl Co-A molecules are

generated in mitochondria. As acetyl CoA cannot pass through inner mitochondrial membrane it undergoes Condensation with oxaloacetate and forms citrate that easily diffuses out of mitochondria.

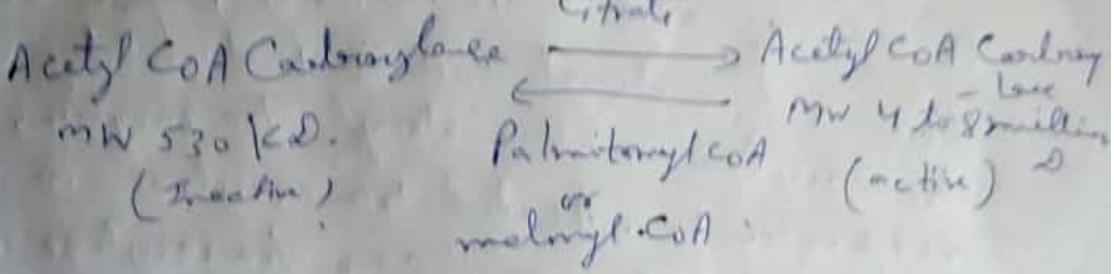
In cytosol, citrate gets cleaved into oxaloacetate and acetyl CoA by the enzyme ATP-citrate lyase utilizing Coenzyme A and ATP. Acetyl CoA is utilized for fatty acid Synthesis but oxaloacetate get converted to malate by malate dehydrogenase utilizing reduced nicotinamide adenine dinucleotide (NADH). Subsequently, malate in the presence of $NADP^+$ and malic enzyme, gets oxidised to Pyruvate. Reduced $NADP^+$ generated is utilised in fatty acid Synthesis.

step 2: Carboxylation of Acetyl CoA to Malonyl CoA – Synthesis of fatty acids begins with condensation of two molecules of acetyl CoA. However, the energy provided by two molecules of acetyl CoA is not sufficient for condensation reaction. To meet the energy requirement, one acetyl Co-A is carboxylated to malonyl CoA by acetyl Co-A Carboxylase enzyme utilising CO_2 and ATP. Malonyl CoA, thus

formed, provides the required energy for carboxylation with the acetyl CoA. The acetyl CoA carboxylase is an allosteric enzyme whose active state is dependent on dephosphorylation and is regulated by the concentration of citrate and palmitoyl CoA.



Carboxylation of acetyl Co-A to malonyl co-A



In bacteria (E. coli), acetyl CoA carboxylase is a multienzyme complex comprising three enzymes: a BCCP, biotin carboxylase and a transcarboxylase.

Reaction begins with carboxylation of biotin linked to BCCP by the enzyme biotin carboxylase, subsequently CO2 from biotin is transferred by transcarboxylase to acetyl CoA forming malonyl CoA.

Step 3: Transfer of Acyl Groups to Acyl Carrier Proteins

→ Malonyl CoA formed in step 2 now combines

with acetyl CoA, but the reaction is not a straight one. The Condensation reaction is preceded by transfer of acyl moieties of acetyl CoA and malonyl CoA to separate acyl carrier protein (ACP). ACP remains linked to all the subsequent metabolites of fatty acid synthesis.

ACP is a single polypeptide of 77 amino acids whose one serine residue is linked to phosphopantetheine group having a terminal -SH group. This thiol group, like the thiol group of coenzyme A, forms a thioester bond with the carbonyl group of acyl moiety of acetyl CoA and malonyl CoA forming acetyl-ACP and malonyl ACP, respectively.

Transfer of acyl moieties to ACP from acetyl CoA and malonyl CoA is induced by acetyl transacylase and malonyl transacylase, respectively. Acetyl transacylase is not very specific and can transacylate even propionyl CoA but malonyl transacylase is highly specific.

Step-4: Condensation of Acetyl-ACP with Malonyl-ACP :- The acetoacyl ACP formed in step 4 is reduced to 3-hydroxybutyryl-ACP by 3-keto acyl-ACP reductase utilizing reduced NADP as hydrogen donor.

The two acyl-ACP molecules (acetyl-ACP and malonyl-ACP) undergo Condensation by the enzyme, β-ketoacyl-ACP

Synthase (also named acyl-malonyl-ACP Condensing enzyme). The reaction first involves transfer of acetyl group from acetyl ACP to the enzyme linking its carbonyl carbon by thioester bond and exiting ACP free. Now, the acetyl group from substrate enzyme complex is shifted to malonyl ACP, which undergoes decarboxylation, and is then left out as acetyl-ACP. The energy from decarboxylation is utilized in Condensation of acetyl group with acetyl ACP forming Aceto-acyl ACP. Acetyl CoA acquires energy from ATP during carboxylation to malonyl CoA & the same energy after decarboxylation of malonyl CoA is utilized for Condensation.

Step 5 → ~~The~~ aceto Reduction of 3-carbonyl group of Acetoacetyl ACP → The acetoacyl ACP formed in step 4 is reduced to 3 hydroxy butyryl-ACP by 3 Keto acyl-ACP reductase utilising reduced NADP as Hydrogen donor.

Step-6 → Dehydration of β-hydroxy butyryl ACP →

The β-hydroxy butyryl ACP formed above loses one H_2O molecule from its carbon-3 by the action of the enzyme 3 hydroxy acyl ACP dehydratase and it converts to crotonyl ACP with the loss of a H_2O molecule, a trans double bond develops between carbon-2 and carbon-3.

Contd... Part II